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# Enterocolic lymphocytic phlebitis of the cecal pole and appendix vermiformis with increase of IgG4-positive plasma cells

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**Abstract** Here we describe the clinicopathological course of a 20-year-old female patient with enterocolic lymphocytic phlebitis (ELP) of the appendix vermiformis and cecal pole with increase of IgG4-positive plasma cells. The patient presented with acute abdomen, suspicious of acute appendicitis. Diagnostic laparoscopy showed tumefaction of the cecal pole and appendix vermiformis. Histologic examination revealed mural thickening and a dense lymphoplasmocytic, partly obliterative infiltrate of the veins with sparing of the arteries, diagnostic of ELP. In addition, we found an elevated number of IgG4-positive plasma cells blended in with the lymphocytes. The IgG4-to-IgG ratio accounted for >40 %. This case meets the histopathological criteria requested for IgG4-related disease (IgG4-RD) and thus opens the possibility that ELP might be part of the IgG4-RD spectrum.

**Keywords** Enterocolic lymphocytic phlebitis (ELP) · Mesenteric inflammatory veno-occlusive disease (MIVOD) · IgG4-related disease (IgG4-RD) · IgG4 · Obliterative phlebitis

## Introduction

Acute appendicitis still is the most common cause of acute abdomen. In contrast, enterocolic lymphocytic phlebitis (ELP), an immunologic disease with unknown etiology and pathophysiology is a rare cause of acute abdomen. ELP affects the mesenteric veins and is characterized by a dense lymphocytic infiltration of the veins with sparing of the concomitant arteries [1,

2]. In the last decade, the new systemic immunologic disease category of IgG4-related diseases (IgG4-RD) was discovered and studied. Diseases such as autoimmune pancreatitis type 1, Mikulicz disease, or retroperitoneal fibrosis (Ormond's disease) fall in this category. Sclerosing mesenteritis has been suggested to fall into the group of IgG4-RD [3]. IgG4-RD show three characteristic histologic features: dense lymphoplasmocytic infiltrate, storiform-type fibrosis, and obliterative phlebitis. In addition, an elevated IgG4 cell count as well as a ratio of IgG4/IgG >40 % are required to make the diagnosis. There are now strict criteria of IgG4-RD because a lot of diseases show elevated numbers of IgG4-positive plasma cells, although they are not part of IgG4-RD [4]. Here, we describe a case of ELP with features of IgG4-RD and discuss whether ELP might be a form of IgG4-RD.

## Clinical history

A 20-year-old female patient presented with acute abdomen and suspected acute appendicitis. Laparoscopic appendectomy was started, but the procedure had to be changed to open appendectomy due to the finding of a conglomerate swelling involving cecal pole and appendix vermiformis.

## Materials and methods

Surgical specimens were fixed in 4 % paraformaldehyde in phosphate-buffered saline and embedded in paraffin. Sections of 2–3 µm were stained with hematoxylin–eosin and van Gieson–elastine as well as immunohistochemical markers such as CD20, CD3, CD4, CD8, IgG, and IgG4. Histologic slides of the appendix vermiformis and cecal pole were scanned and reviewed. The IgG4-to-IgG ratio was independently determined by two pathologists (S. C. and J. F.) by

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choosing three different areas with the highest density of IgG4 and manually counting both IgG4 and IgG in three high-power fields (HPFs). The ratio was determined from the average of each count of IgG4 and IgG. Follow-up of the patient comprised 18 months after surgery. The patient's consent was obtained for this study.

## Results

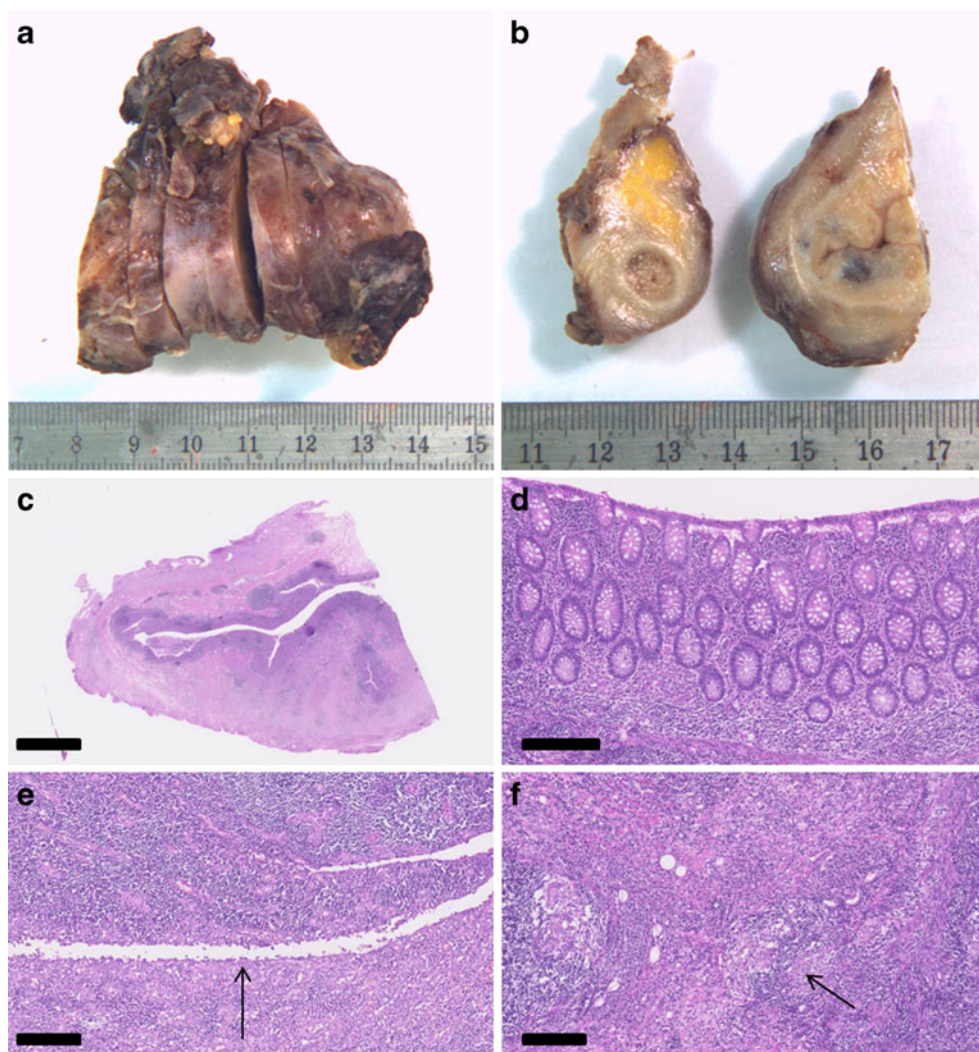
### Pathologic findings

The specimen consisted of the appendix vermiformis with adherent cecal pole and adipose tissue of 10.5 cm length, 5.5 cm width, and 3 cm depth. It was of firm consistency with partly a smooth and glistening serosal surface and partly whitish brown plaques and showed a tumefaction of the appendix extending to the cecal pole (pseudotumor; Fig. 1a). The cut surface revealed an obliterated lumen of 2 cm in diameter (Fig. 1b). Microscopically, the bowel wall was

thickened (Fig. 1c), and the mucosa was mostly normal, i.e., not inflamed epithelium (Fig. 1d). There was an intramural fissure (Fig. 1e), but no significant architectural disarray. However, a transmural chronic inflammation was found including the serosa along with mural fibrosis/thickening and few small granulomas (Fig. 1f). Since histology revealed no evidence of an acute appendicitis, other differential diagnoses had to be considered such as Crohn's disease, sarcoidosis, foreign body reaction, or various infections, in particular Yersiniosis. Further histologic investigations revealed the following characteristics: a dense cuff-like lymphocytic infiltrate around the veins of the submucosa and the adventitia of the bowel wall. Veins were partly destroyed or obliterated, whereas accompanying arteries were unremarkable and spared (Fig. 2a–d). Immunostains revealed mostly CD3- and CD4-positive lymphocytes, whereas CD8- and CD20-positive lymphocytes were less numerous (Fig. 2e–h). Based on the clinical and pathological findings, a diagnosis of ELP was made.

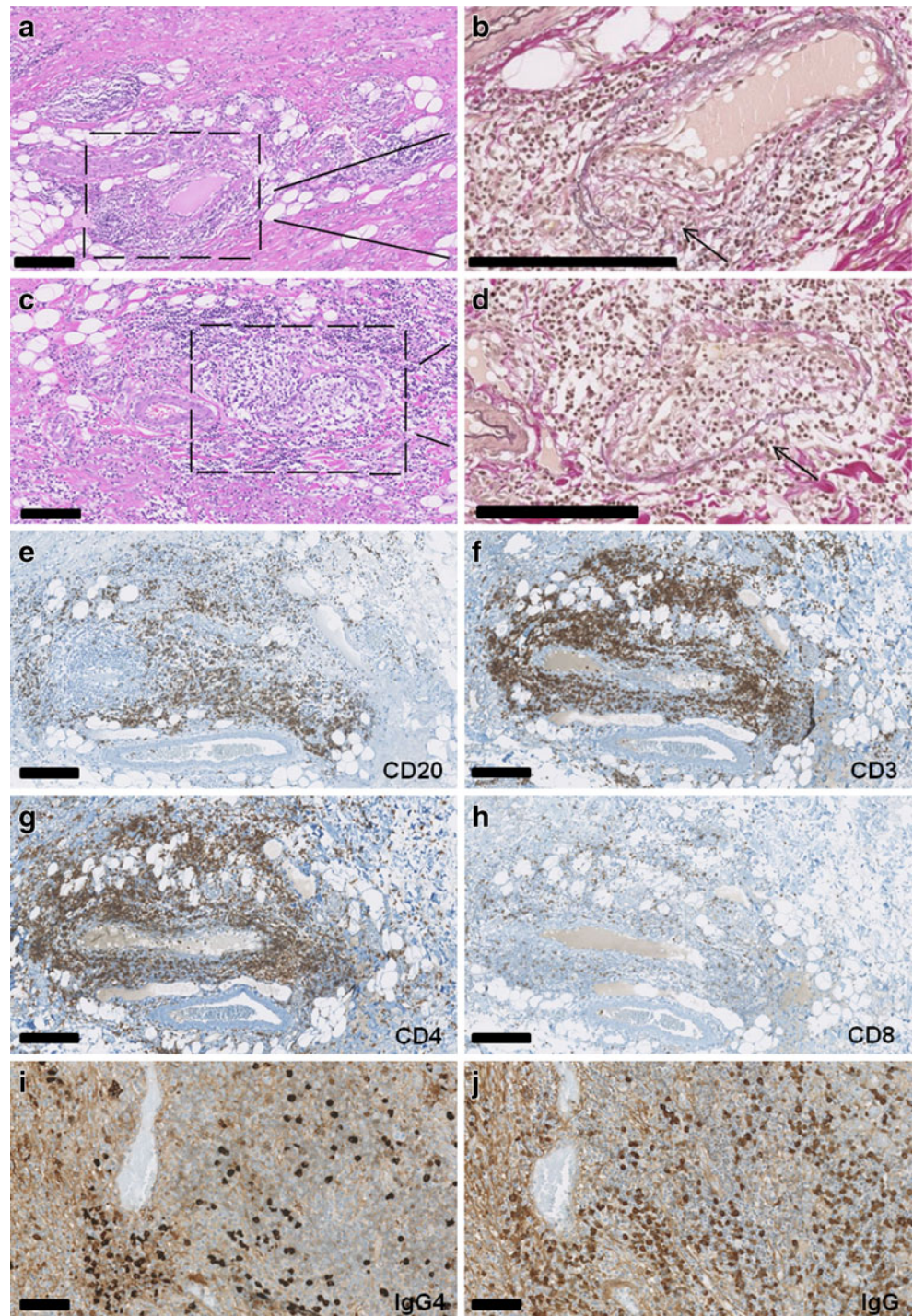
The striking phlebitis in combination with multifocal dense plasma cell infiltrates prompted us to stain for IgG4. Numerous

**Fig. 1** **a** Gross specimen with the cecal pole and appendix vermiformis forming a conglomerate (pseudo) tumor. **b** Cut surface of gross specimen. **c** Cecal pole, histologic overview: thickening of the bowel wall (scale bar 2.5 mm). **d** Appendiceal mucosa without inflammation (scale bar 200  $\mu$ m). **e** Intramural fissure (scale bar 200  $\mu$ m). **f** Granuloma formation (scale bar 200  $\mu$ m)





**Fig. 2** **a, b** Dense lymphocytic infiltrate surrounding a vein like a cuff with sparing of the artery (**a** HE, scale bar 200  $\mu$ m; **b** EvG, scale bar 200  $\mu$ m). **c, d** Obliteration and destruction of the vein through lymphocytes with sparing of the artery (**c** HE, scale bar 250  $\mu$ m; **d** EvG, scale bar 200  $\mu$ m). **e** The staining with CD20 showed a moderate infiltrate of B lymphocytes (scale bar 200  $\mu$ m). **f** The staining with CD3 showed a marked infiltrate of T lymphocytes (scale bar 200  $\mu$ m). **g** Numerous CD4-positive cells (scale bar 200  $\mu$ m) and **h** few CD8-positive lymphocytes (scale bar 200  $\mu$ m). **i** Numerous IgG4-positive cells predominantly around the veins (scale bar 100  $\mu$ m). **j** IgG-positive cells, diffusely distributed (scale bar 100  $\mu$ m)



IgG4-positive plasma cells were found around the veins (Fig. 2i, j). The IgG4-to-IgG ratio accounted for >40 %, measured in a similar manner as proposed by Shrestha et al. [5]. IgG and IgG4 counts were independently determined by two pathologists, and the ratio accounted for 41.5 and 49 %, respectively.

Detailed retrospective inquiries about the patient's history revealed no further information on the etiology of the pathologic

findings; in particular, there were no previous symptoms or signs of IBD or autoimmune disease and no family history of IBD or autoimmune disease. The patient took oral contraceptives (OC) and consumed cannabis from time to time.

Follow-up took place six weeks later. The patient was clinically fine and colonoscopy and biopsies (terminal ileum and colon, not shown) turned out unremarkable. Eighteen months after the initial presentation, the patient still is without complaint.

## Discussion

ELP [1, 2], also referred to as “mesenteric inflammatory veno-occlusive disease” (MIVOD), is a localized disease of small- and medium-sized submucosal, subserosal, and mesenteric veins of the bowel wall. The veins are surrounded or obstructed by a dense lymphocytic infiltrate. The arteries and arterioles as well as the systemic circulation typically are spared. Etiology and pathogenesis of this rare disease are unknown. Patients present mostly with signs of acute abdomen. The diagnosis is established only by histologic examination of the resected bowel segment. Mucosal biopsies are inadequate. Surgery is generally curative and the prognosis excellent. Relapses are unusual.

The phlebitis and plasma cells as well as the tumor-like lesion of the involved organs reminded us of IgG4-RD, a systemic disease, which typically shows high levels of IgG4 found in blood serum. Histologically, three hallmarks are characteristic for this disease, including obliterative phlebitis. The other two pathological features are a dense lymphoplasmocytic infiltrate and a storiform-type of fibrosis, respectively. Only in 2012, clinical and pathological guidelines were established, and an algorithm was proposed for the diagnosis of IgG4-RD. There are additional conditions required to establish IgG4-RD in a new organ/site [4]. This case meets the first of the four requested criteria, i.e., the histopathological findings. The three clinical criteria required could not be achieved for different reasons. IgG4 concentrations in blood serum were not measured at the time of admission to hospital. Then, the patient underwent surgery, so that a glucocorticoid therapy was not indicated. Therefore, these two points cannot be evaluated in

this case. As regards the last point, no other organ/site has been involved so far.

## Conclusion

To our knowledge, this is the first case of ELP with elevated IgG4-positive plasma cells. The case presented here met the histopathological criteria for IgG4-RD, opening the possibility that ELP might be part of the IgG4-RD spectrum.

**Conflict of interest** The authors declare that they have no conflict of interest.

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